

Claims

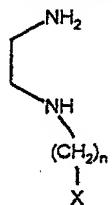
1. Transferrin, albumin and polyethylene glycol conjugates, obtainable by coupling a
2 derivatized cytostatic compound, consisting of the cytostatic compound and a
3 spacer molecule having a maleimide group, to thiolated transferrin or albumin
4 having on the average from 1 to 30 HS groups or to polyethylene glycol having, at
5 least, one HS or H₂N group and having a mass of about between 5,000 and
6 200,000 Da, wherein about from 1 to 30 molecules of the derivatized cytostatic
7 compounds are bound to one molecule of transferrin, albumin or polyethylene
8 glycol,
9 or by coupling a derivatized cytostatic compound, consisting of the cytostatic
10 compound and a spacer molecule having a N-hydroxysuccinimide ester group, to
11 thiolated transferrin or albumin having on the average from 1 to 30 HS groups or
12 to the polyethylene glycol having, at least, one HO- or H₂N- group and having a
13 mass of about between 5,000 and 200,000 Da, wherein about from 1 to 30
14 molecules of the derivatized cytostatic compounds are bound to one molecule of
15 transferrin, albumin or polyethylene glycol,
16 or obtainable by loading thiolated albumin with from 2 to 30 equivalents of the
17 derivatized cytostatic compound, consisting of the cytostatic compound and a
18 spacer molecule having a maleimide group, and conjugating with transferrin or a
19 monoclonal antibody which is directed against a tumor-associated antigen, via a
20 bismaleimide compound.

1. Transferrin, albumin and polyethylene glycol conjugates according to claim 1,
2 obtainable by coupling a derivatized cytostatic compound, consisting of a
3 cytostatic compound from the group of the anthracyclines, the nitrogen mustard
4 gas derivatives, the purine or pyrimidine antagonists, the folic acid antagonists, the
5 taxoids, the camptothecines, the podophyllotoxin derivatives, the vinca alkaloids
6 or the *cis*-configured platinum(II)-complexes, respectively, and a spacer molecule
7 having a maleimide group, to thiolated transferrin or albumin having on the

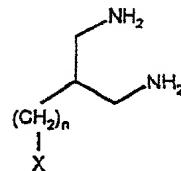
average from 1 to 30 HS groups or to polyethylene glycol having, at least, one HS or H₂N group and having a mass of about between 5,000 and 200,000 Da, wherein about from 1 to 30 molecules of the derivatized cytostatic compounds are bound to one molecule of transferrin, albumin or polyethylene glycol, or by coupling a derivatized cytostatic compound, consisting of the cytostatic compound from the group of the anthracyclines, the nitrogen mustard gas derivatives, the purine or pyrimidine antagonists, the folic acid antagonists, the taxoids, the camptothecines, the podophyllotoxin derivatives, the vinca alkaloids or the *cis*-configured platinum(II)-complexes and a spacer molecule having a N-hydroxysuccinimide ester group, to thiolated transferrin or albumin having on the average from 1 to 30 HS groups or to the polyethylene glycol having, at least, one HO- or H₂N- group and having a mass of about between 5,000 and 200,000 Da, wherein about from 1 to 30 molecules of the derivatized cytostatic compounds are bound to one molecule of transferrin, albumin or polyethylene glycol, or by loading thiolated albumin with from 2 to 30 equivalents of the derivatized cytostatic compound, consisting of the cytostatic compound from the group of the anthracyclines, the nitrogen mustard gas derivatives, the purine or pyrimidine antagonists, the folic acid antagonists, the taxoids, the camptothecines, the podophyllotoxin derivatives, the vinca alkaloids or the *cis*-configured platinum(II)-complexes, respectively, and a spacer molecule having a maleimide group, and conjugating with transferrin or a monoclonal antibody, which is directed against a tumor-associated antigen, via a bismaleimide compound.

3. Transferrin, albumin and polyethylene glycol conjugates, according to anyone of the preceding claims, obtainable by reacting
 - a). doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxandron, chlorambucil, melphalan, 5-fluorouracil, 5'-desoxy-5-fluorouridine, thioguanine, methotrexate, paclitaxel, docetaxel, topotecane, 9-aminocamptothecine, etoposide, teniposide, mitopodoside, vinblastine, vincristine, vindesine, vinorelbine or a compound of the general formula I, II, III or IV:

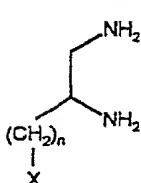
Formula I



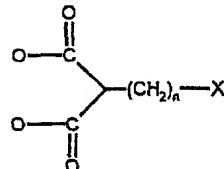
Formula II



Formula III



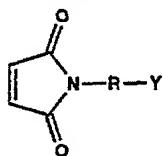
Formula IV



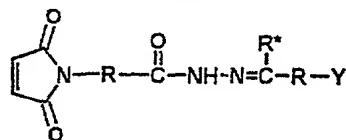
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n = 0 – 6, X = -NH₂, -OH, -COOH, -O-CO-R-COR*, -NH-CO-R-COR*, wherein R is an aliphatic carbon chain with 1 – 6 carbon atoms or a substituted or unsubstituted phenylene group and R* is H, phenyl, alkyl with 1 – 6 carbon atoms, and the amine functions are provided with a protective group such as the *tert*-butyloxycarbonyl protective group,

with a maleimide compound of the general formula V, VI or VII

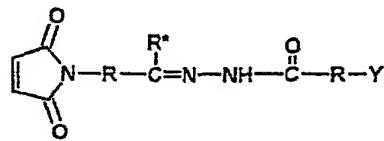
Formula V



Formula VI



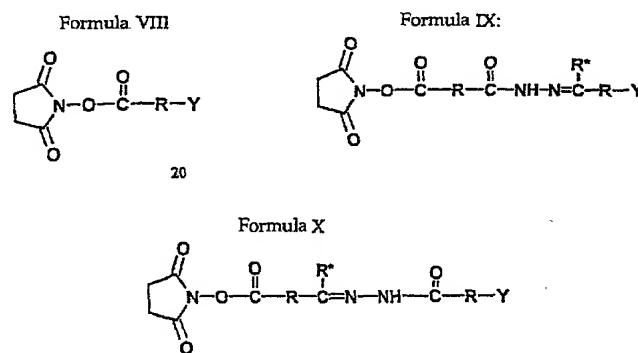
Formula VII



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wherein, in the case that R is an aliphatic carbon chain with 1 – 6 carbon atoms,
Y = -OH, -COOH, -COCl, -CONH-(CH₂)_n-OH, -COO-(CH₂)_n-NH₂, -COO-(CH₂)_n-
NHNH₂, -SO₃H, -SO₃Cl, -SO₂-NHNH₂, -O-COCl, -CHO, COR* with n = 1 – 6
and R* = H, phenyl, alkyl with 1 – 6 carbon atoms, and wherein, in the case that R

18 is a substituted or unsubstituted benzyl group or a substituted or unsubstituted
 19 phenylene group, Y = -OH, -COOH, -COCl, -CONH-(CH₂)_n-OH, -COO-(CH₂)_n-
 20 NH₂, -COO-(CH₂)_n-NHNH₂, -SO₃H, -SO₃Cl, -SO₂-NHNH₂, -O-COCl, -CHO, -
 21 COR*, -CO-NHNH₂ with n = 1 - 6 and R* = H, phenyl, alkyl with 1 - 6 carbon
 22 atoms,

23 or with an N-hydroxysuccinimide compound of the general formula VIII, IX or X



24 wherein R is a substituted or unsubstituted phenylene group, Y = -OH, -NH₂, -
 25 NHNH₂, -COOH, -COCl, -COO-(CH₂)_n-OH, -CONH-(CH₂)_n-NH₂, -COO-(CH₂)_n-
 26 NHNH₂, -SO₃H, -SO₃Cl, -SO₂-NHNH₂, -O-COCl, -CHO, -COR*, -CO-NHNH₂
 27 with n = 1 - 6 and R* = H, phenyl, alkyl with 1 - 6 carbon atoms,
 28 wherein, in the derivatives obtained from the compounds of the general formula I,
 29 II or III, the protective group is removed and the thus-obtained amines are reacted
 30 with a tetrachloroplatinate salt to yield the corresponding *cis*-configured
 31 platinum(II)-complexes, and wherein the derivatives obtained from the
 32 compounds of the general formula IV are reacted with *cis*-[PtA₂B] (A = halogen,
 33 B = (NH₃)₂, ethylene diamine, propane diamine, 1,2-diaminocyclohexane) to yield
 34 the corresponding platinum(II)-complexes,

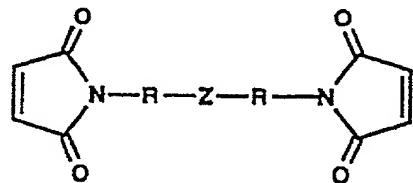
35 so that maleimide derivatives or N-hydroxysuccinimide ester derivatives of
 36 cytostatic compounds are provided, wherein the chemical linkage occurs between

37 the cytostatic compound and the maleimide compound or N-
 38 hydroxysuccinimide compound, respectively, through an amide, ester, imine,
 39 hydrazone, carboxylhydrazone, oxycarbonyl, acetal or ketal bond, and

40 b). the thus-obtained maleimide derivative is coupled to thiolated transferrin or
 41 albumin with on the average from 1 to 30 HS groups or to polyethylene glycol
 42 having, at least, one HS- or H₂N group and having a mass of between about 5,000
 43 and 200,000 Da, wherein about from 1 to 30 molecules of the maleimide
 44 derivatives obtained in Step a) are bound to one molecule of transferrin, albumin
 45 or polyethylene glycol,

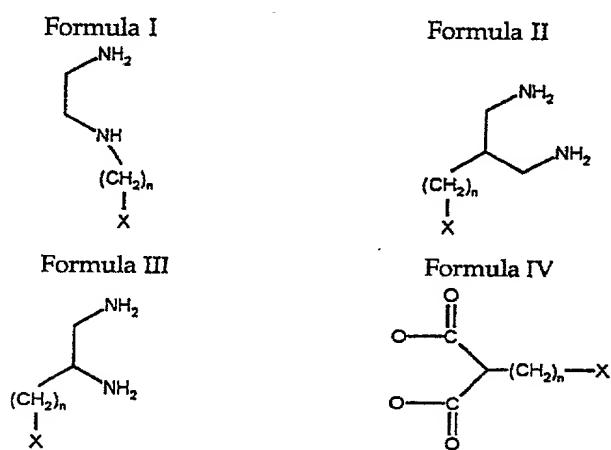
46 or the thus-obtained N-hydroxysuccinimide ester derivative is coupled to
 47 transferrin or albumin or to polyethylene glycol having, at least, one HO- or H₂N
 48 group, having a mass of between approximately 5,000 and 200,000 Da, wherein
 49 about 1 to 30 molecules of the N-hydroxysuccinimide derivatives obtained in Step
 50 a) are bound to one molecule of transferrin, albumin or polyethylene glycol,

51 or by loading thiolated albumin with from 2 to 30 equivalents of the maleimide
 52 derivatives obtained in Step a) and conjugating with transferrin or a monoclonal
 53 antibody which is directed against a tumor-associated antigen, via a
 54 bismaleimide compound of the general formula XI



55 Z = -CO-NH-(CH₂)_n-NH-CO-, -CO-O-(CH₂)_n-O-CO-, -C=NH-(CH₂)_n-NH=C-, -
 56 C=N-NH-(CH₂)_n-NH-N=C-, -C=N-NH-CO-(CH₂)_n-CO-NH-N=C-, n = 2 - 12.

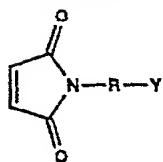
1 4. Method for the production of transferrin, albumin and polyethylene glycol
 2 conjugate, according to anyone of the preceding claims, characterized in that
 3 a). doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxandrone, chloroambucil,
 4 melphalan, 5-fluorouracyl, 5'-desoxy-5-fluorouridine, thioguanine, methotrexate,
 5 paclitaxel, docetaxel, topotecane, 9-aminocamptothecine, etoposide, teniposide,
 6 mitopodoside, vinblastine, vincristine, vindesine, vinorelbine or a compound of
 7 general the formula I, II, III or IV:



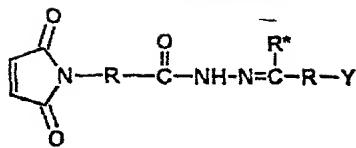
8 n = 0 – 6, X = -NH₂, -OH, -COOH, -O-CO-R-COR*, -NH-CO-R-COR*, wherein
 9 R is an aliphatic carbon chain with 1 – 6 carbon atoms or a substituted or
 10 unsubstituted phenylene group and R* is H, phenyl, alkyl with 1 – 6 carbon
 11 atoms, and the amine functions are provided with a protective group such as the
 12 *tert*.-butyloxycarbonyl protective group,

13 with a maleimide compound of the general formula V, VI or VII

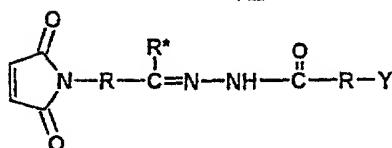
Formula V



Formula VI



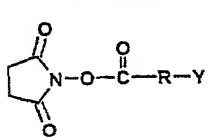
Formula VII



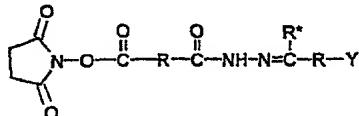
wherein, in the case that R is an aliphatic carbon chain with 1 – 6 carbon atoms, Y = -OH, -COOH, -COCl, -CONH-(CH₂)_n-OH, -COO-(CH₂)_n-NH₂, -COO-(CH₂)_n-NHNH₂, -SO₃H, -SO₃Cl, -SO₂-NHNH₂, -O-COCl, -CHO, -COR* with n = 1 – 6 and R* = H, phenyl, alkyl with 1 – 6 carbon atoms, and wherein, in the case that R is a substituted or unsubstituted benzyl group or a substituted or unsubstituted phenylene group, Y = -OH, -COOH, -COCl, -CONH-(CH₂)_n-OH, -COO-(CH₂)_n-NH₂, -COO-(CH₂)_n-NHNH₂, -SO₃H, -SO₃Cl, -SO₂-NHNH₂, -O-COCl, -CHO, -COR* with n = 1 – 6 and R* = H, phenyl, alkyl with 1 – 6 carbon atoms,

or with an N-hydroxysuccinimide compound of the general formulas VIII, IX or X

Formula VIII

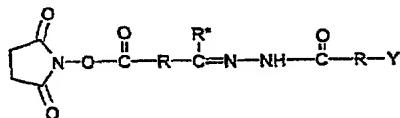


Formula IX:



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Formula X

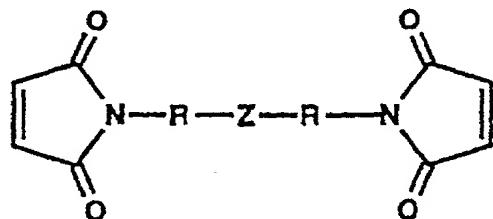


25 NHNH₂, -SO₃H, -SO₃Cl, -SO₂-NHNH₂, -O-COCl, -CHO, -COR*, -CO-NHNH₂
26 with n = 1 - 6 and R* = H, phenyl, alkyl with 1 - 6 carbon atoms,
27 wherein, in the derivatives obtained from the compounds of the general formula I,
28 II or III, the protective group is removed and the thus-obtained amines are reacted
29 with a tetrachloroplatinate salt to yield the corresponding *cis*-configured
30 platinum(II)-complexes, and wherein the derivatives obtained from the
31 compounds of the general formula IV are reacted with *cis*-[PtA₂B] (A = halogen,
32 B = (NH₃)₂, ethylene diamine, propane diamine, 1,2-diaminocyclohexane) to yield
33 the corresponding platinum(II)-complexes,

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50 so that maleinimide derivatives or N-hydroxysuccinimide ester derivatives of
 cytostatic compounds are provided, wherein the chemical linkage occurs between
 the cytostatic compound and the maleinimide compound or N-
 hydroxysuccinimide compound through an amide, ester, imine, hydrazone,
 carboxylhydrazone, oxycarbonyl, acetal or ketal bond, and

b.) the thus-obtained maleinimide derivative is coupled to thiolated transferrin or
 albumin having from 1 to 30 HS groups on the average or to polyethylene glycol
 having, at least, one HS- or H₂N group and having a mass of between about 5,000
 and 200,000 Da, wherein about from 1 to 30 molecules of the maleinimide
 derivatives obtained in Step a) are bound to one molecule of transferrin, albumin
 or polyethylene glycol,
 or the thus-obtained N-hydroxysuccinimide ester derivative is coupled to
 transferrin or albumin or to polyethylene glycol having, at least, one HO- or H₂N
 group, having a mass of between approximately 5,000 and 200,000 Da, wherein
 about from 1 to 30 molecules of the N-hydroxysuccinimide derivatives obtained
 in Step a) are bound to one molecule of transferrin, albumin or polyethylene
 glycol,

51 or by loading thiolated albumin with from 2 to 30 equivalents of the maleimide
52 derivatives obtained in Step a) and conjugating with transferrin or a monoclonal
53 antibody which is directed against a tumor-associated antigen, via a
54 bismaleimide compound of the general formula XI



55 $Z = -CO-NH-(CH_2)_n-NH-CO-, -CO-O-(CH_2)_n-O-CO-, -C=NH-(CH_2)_n-NH=C-, -$
56 $C=N-NH-(CH_2)_n-NH-N=C-, -C=N-NH-CO-(CH_2)_n-CO-NH-N=C-, n = 2 - 12.$

1. Pharmaceutical composition containing a compound according to anyone of the claims 1 to 3 optionally together with usual carriers and auxiliary agents.

2. Use of the transferrin, albumin and polyethylene glycol conjugates according to anyone of the claims 1 to 3 for the treatment of cancer diseases.